Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 2015;372:803-13. DOI: 10.1056/NEJMoa1414850

SUPPLEMENTARY APPENDIX

Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

Authorship: George Du Toit, M.B., B.Ch., M. Med., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B.B.S., M.Sc., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*

The authors affiliations are as follows: Department of Pediatric Allergy, Division of Asthma, Allergy and Lung Biology, King's College London and Guy's and St. Thomas' National Health Service Foundation Trust, London (G.D.T., S.R., A.F.S., H.A.B., M.B., M.F., V.T., G.L.), and the University of Southampton and National Institute for Health Research Respiratory Biomedical Research Unit, Southampton and David Hide Centre, Isle of Wight (G.R.) — both in the United Kingdom; the Division of Hematology–Oncology, Department of Medicine (P.H.S.), and the Immune Tolerance Network (D.P.), University of California, San Francisco; Rho Federal Systems Division, Chapel Hill, NC (H.T.B., M.L.S.), and the National Institute of Allergy and Infectious Diseases, Bethesda, MD (M.G.L., M.P.).

Members of the LEAP Study Team include:

Clinical support: Rosa Caballero, Susan Chan, Adam Fox. **Nursing Staff:** Mable Abraham, Muhsinah Adam, Lyn Clough, Louise Coverdale, Helen Fisher, Fiona Henley, Saadia Hussain, Victoria Johnston, Amy Nixon, Una O'Dwyer-Leeson, Aine Sheridan. **Dietitians:** Tammy Amarra, Kathryn Cockerell, Sarah Lacey, Gail Harland, Charlotte Stedman, Ruth Towell. **Study management and administration:** Catherine Clarke, Richard Cleaver, Gemma Deutsch, Erica Harris, Lori Nirenstein, Alicia Parr. **Laboratory projects:** Natalia Becares, Matthew Crossley, Natalia do Couto Francisco, Kerry Richards, Deeviya Patel, Ewa Pietraszewicz, Alick Stephens, Asha Sudra, Rianne Wester, Alastair Wilson, Celine Wu. **Play Specialists:** Jenna Heath, Kathryn Hersee. **Phlebotomist:** Devi Patkunam. **ITN Staff**: Michael Adamkiewicz, Adam Asare, Eduard Chani, Judith Evind, Kristina Harris, Noha Lim, Nariman Nasser, Audrey Plough, Jennifer Romaine, Michael Stahly. **NIAID Staff:** Joy Laurienzo Panza. **Rho Federal Systems Staff:** Kaitie Fernandez, Susan McCachren, Travis Mason, Valerie Nelson.

Table of Contents

1. Supplement to the Methods 3

Enrollment and Study Procedures: Definition of Severe Eczema 3

2. Supplement to the Results 3

Peanut Consumption Prevents Allergy in Children: Analysis of Primary and Secondary Prevention 3

Compliance and Safety: Participants Who Discontinued Peanut Consumption 3

3. Supplement to the Discussion 4

Compliance and Safety 4

4. Supplementary Figures 5

Figure S1. Diagnostic Algorithm for Determination of Peanut Allergy in the Absence of Peanut-Challenge Results Using Dietary and Reaction History, SPT, and Peanut-Specific IgE. 5

Figure S2. Peanut Protein in Bed Dust at 60 Months of Age 6

Figure S3. Adverse Event Volcano Plot 7

Figure S4. Proportion Density Plot 8

Figure S5. Contour Scatter Plots of Peanut-specific IgG4 versus Peanut-specific IgE at 4-11, 12, 30 and 60 Months of Age 9

5. Supplementary Tables 10

Table S1. Leap Study Schedule of Events 10

Table S2. Baseline Characteristics 11

Table S3. Primary and Secondary Prevention for Different Levels of Sensitization 12

Table S4. Peanut Protein Consumption (grams) by Randomized Group and Stratum 13

Table S5. Peanut Protein in Bed Dust at 60 Months of Age by Stratum 14

Table S6. All Cause Hospitalizations and Mortality 15

Table S7. Serious Adverse Events 16

Table S8. Adverse Events - Poisson Analysis 20

Table S9. Adverse Events of Interest 25

Table S10. Participants Who Discontinued Peanut Consumption 31

Table S11. Clinical Symptoms and Medication Requirements Associated with Positive Oral Food Challenges 33

Table S12. Primary Outcome by Race 35

1. SUPPLEMENT TO THE METHODS

Enrollment and Study Procedures: Definition of Severe Eczema

Severe eczema was defined in the protocol eligibility criteria and defined in one of three ways. The study definition for severe eczema is described in the Protocol under Study definitions Section 3.5. and is as follows:

- A rash that required the application of a topical creams and ointments containing corticosteroids or calcineurin inhibitors and if the participant is:
    - <6 months of age, lasted for at least 12 out of 30 days on two occasions, or
    - >6 months of age, lasted for at least 12 out of 30 days on two occasions in the last 6 months; or
- Has been described by the participant's parent or guardian in a pre-enrollment questionnaire as "a very bad rash in joints and creases" or "a very bad itchy, dry, oozing, or crusted rash"; or
- Is currently or was previously graded ≥ 40 using the modified SCORAD evaluation.

2. SUPPLEMENT TO THE RESULTS

Peanut Consumption Prevents Allergy in Children: Analysis of Primary and Secondary Prevention

The LEAP study was conceived as two independently powered studies to examine the effects of intervention in an SPT negative group who are presumed to be non peanut sensitized and a peanut sensitized SPT positive group. The SPT negative group is described in the manuscript as 'the cohort with negative results on the initial skin-prick test' and the SPT positive group as 'the cohort with positive results on the initial skin-prick test'. It emerged early in the study that a high percentage of children who were SPT negative already showed serological evidence of IgE sensitization to peanut. Thus there are two levels of sensitization; firstly sensitization with IgE production in the serum, and secondly SPT positive sensitization where IgE is bound to cutaneous mast cells.

Our primary endpoint analyses were conducted independently on the SPT-negative and SPT-positive strata as per our statistical analysis plan. However we performed further analyses to distinguish between primary and secondary effects. In order to examine primary prevention, we looked at the efficacy of intervention in infants who were both SPT negative and specific IgE negative (<0.1kU$_A$/L). The supplementary table (Table S3) shows how we are able to look at primary prevention vs secondary prevention in children with exclusively serological sensitization and secondary prevention in children with both serological and SPT positive sensitization.

Compliance and Safety: Participants Who Discontinued Peanut Consumption

At baseline, Oral Food Challenges (OFC) were undertaken for all participants randomized to the peanut group (n=319). All but 7 of these OFCs were negative; of the participants with a positive OFC, 6 were in the SPT-positive stratum and one in the SPT-negative stratum. The symptom presentation, and medication requirement, for these seven positive baseline OFCs are detailed in **Table S11.** There were no SAE's reported.

There were 9 participants with a negative baseline OFC who subsequently discontinued peanut consumption. Only one of these participants met the criteria for per-protocol peanut consumption. A peanut-induced SAE was reported for one of these 9 participants. **Table S10** provides the clinical details of these 9 participants including stratum, age of discontinuation of peanut ingestion, symptoms that influenced the decision to stop ingesting peanut, and month 60

outcome. As shown in the table, several of these participants had an unscheduled visit (USV) to evaluate more fully their symptoms.

There were 3 OFCs undertaken at USVs; no SAEs were reported.

There were 617 OFCs undertaken at V60 of which 57 were positive. The clinical symptoms and medication requirements for all positive OFCs are detailed in **Table S11.**

3. SUPPLEMENT TO THE DISCUSSION

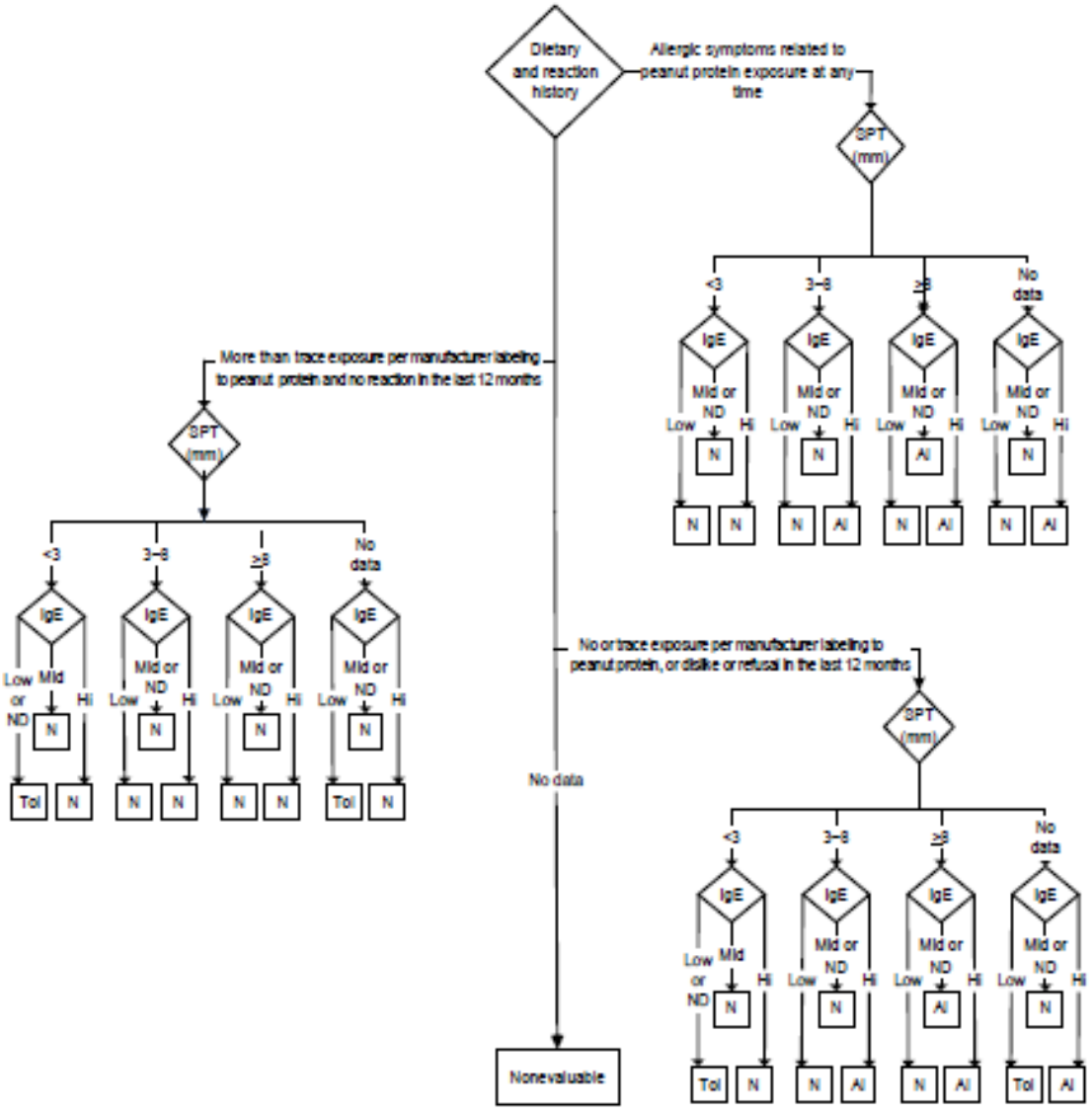
Compliance and Safety

Although there was no difference in the rate of serious adverse events between the two groups, we did note an increase in the total number of adverse events in the consumption group which cannot easily be accounted for. This could represent a real association with the intervention, or alternatively could reflect a reporting bias due to the unblinded study design. It is noteworthy that the reactions reported more frequently in the consumption group generally relate to symptoms that patients perceive to be a consequence of food allergy or food intolerance, such as rashes or gastrointestinal complaints. Given that this excess of reactions was not IgE-associated; this could reflect either non-IgE mediated immunological pathways or parental concern due to the nature of the intervention. It should be noted, however, that this excess of adverse events generally comprised mild and moderate symptoms and we believe is outweighed by the burden of peanut allergy in the population that did not undergo the intervention.

4. SUPPLEMENTARY FIGURES

Figure S1. Diagnostic Algorithm for Determination of Peanut Allergy in the Absence of Peanut-Challenge Results Using Dietary and Reaction History, SPT, and Peanut-Specific IgE.

An oral food challenge was used for the assessment of peanut allergy for 96% (617 of 640) of participants; this diagnostic algorithm was therefore required for 13 study participants whose outcomes were as follows: 7 were peanut allergic, 4 were peanut tolerant and 2 were non-evaluable.



LEGEND

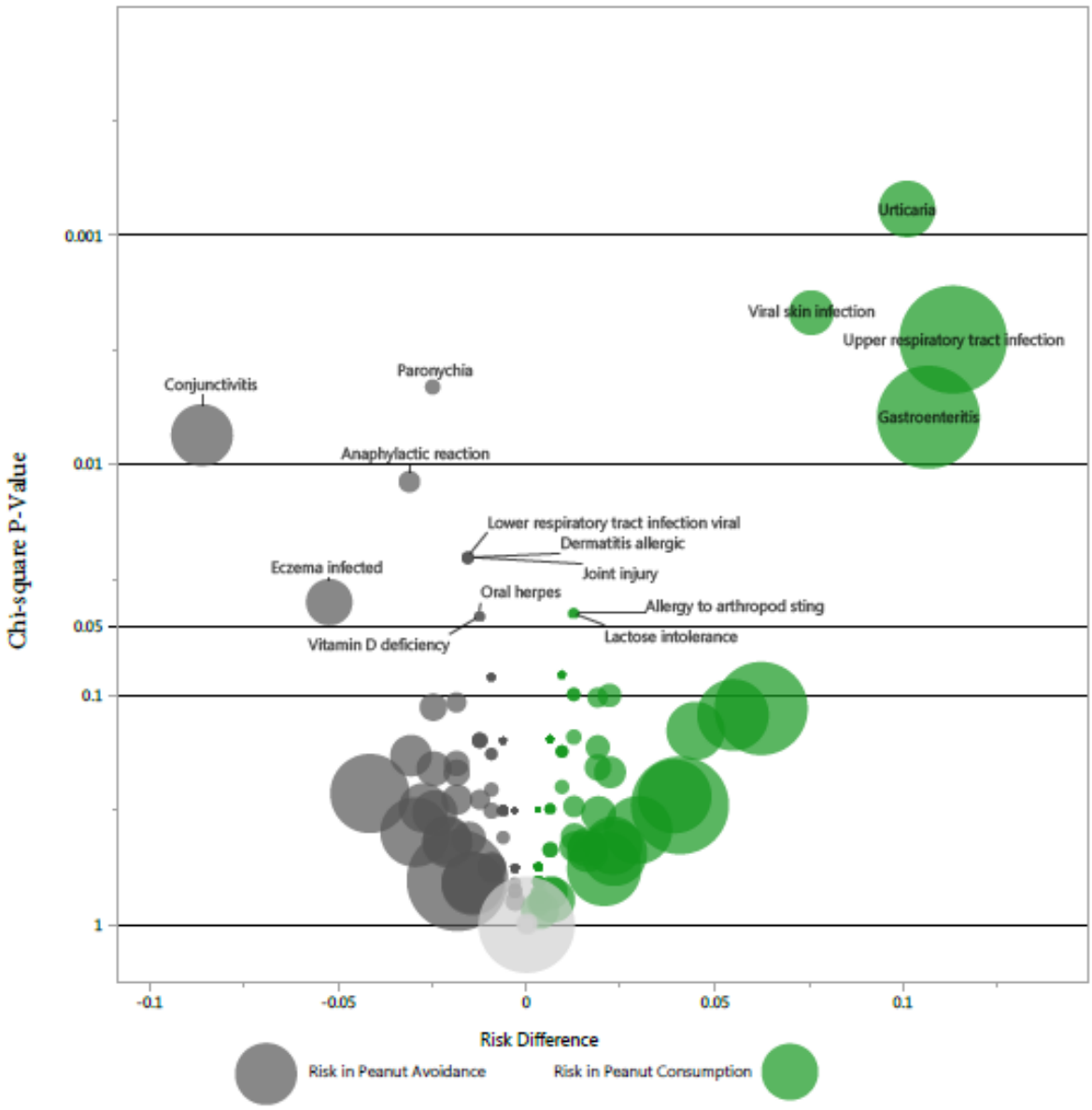
IgE Levels in kU$_A$/L
Low: < 0.35
Mid: ≥ 0.35 and < 15
Hi: ≥15
ND: No data

Tol: tolerant
Al: allergic
N: nonevaluable

Figure S2. Peanut Protein in Bed Dust at 60 Months of Age

Peanut protein levels (mcg/g, log10 transformed units) are shown from dust collected from individual participant's bed sheets who provided samples at 60 months. These represent data from subjects in the peanut avoidance group (N=218), in black, and the peanut consumption group (N=205), shown in green. The box in the box and whisker plots represents the median and IQR. The whiskers represent the furthest point within 1.5 times the IQR from the box.

Figure S3. Adverse Event Volcano Plot



These analyses are performed on the preferred term categorization, which is a coded version of the verbatim term using the Medical Dictionary for Regulatory Activities (MedDRA). The sizes of the bubbles are proportional to the number of subjects having the preferred term. The risk difference is displayed on the x-axis and is calculated by subtracting the incidence of the preferred term between the randomized groups. The y-axis displays chi-square p-values.

All AE and SAE data are also available in an interactive explorer at http://graphics.rhoworld.com/studies/leap/aes/explorer/.

Figure S4. Proportion Density Plot

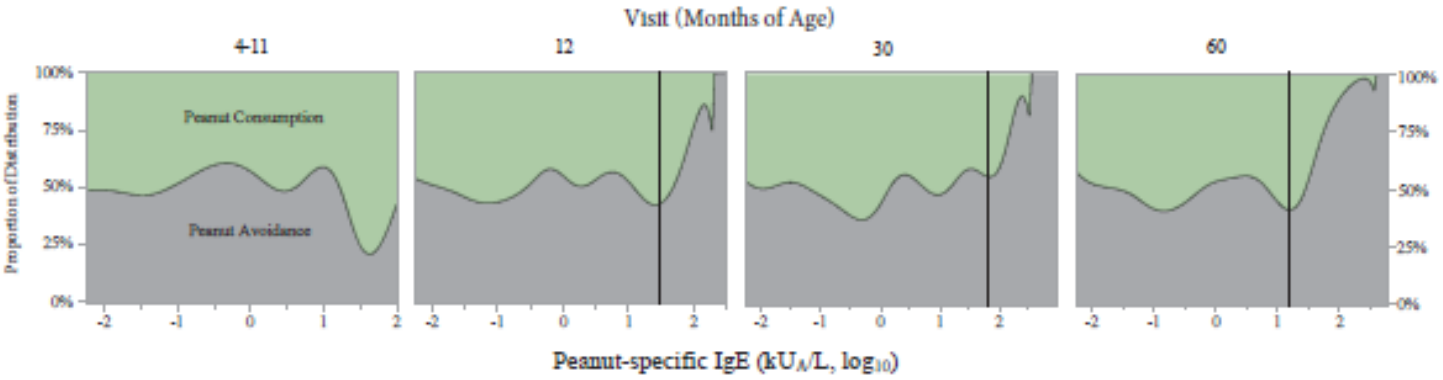
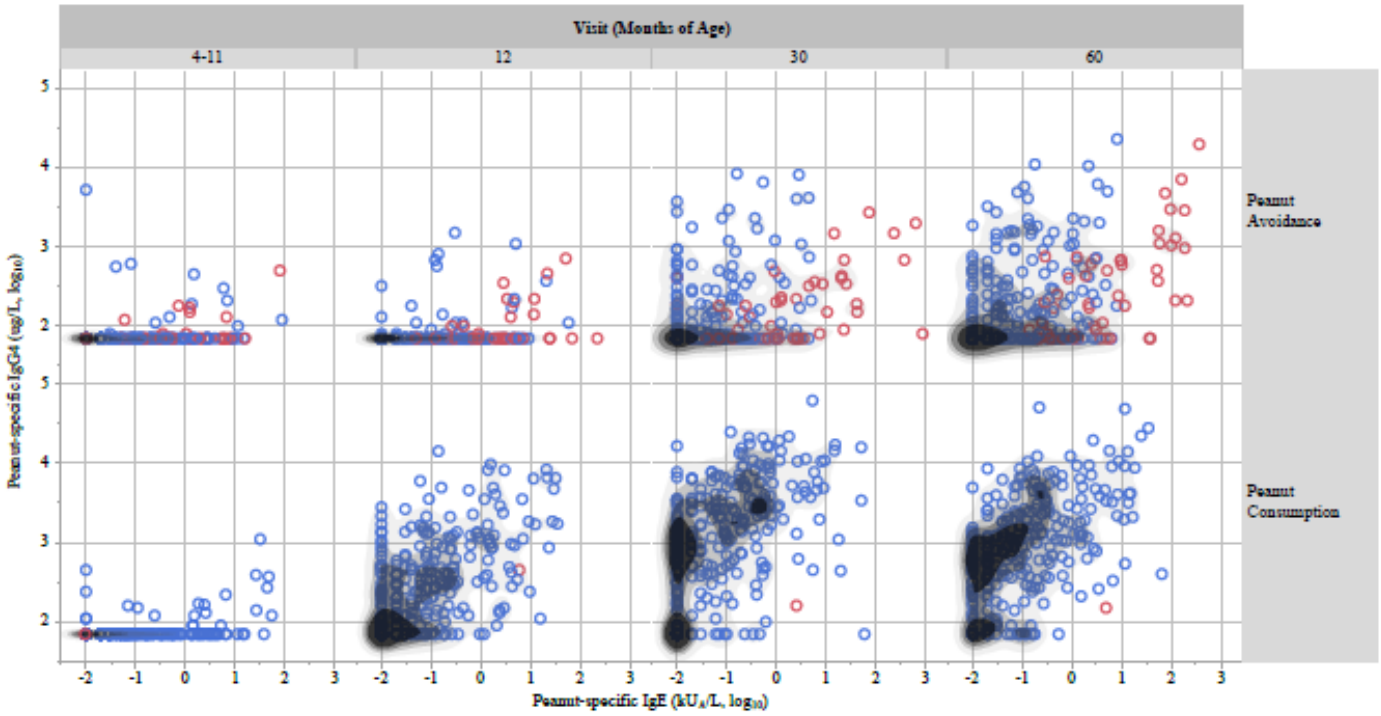


Figure S4 shows the relative distribution of peanut-specific IgE between the peanut consumption (shown in green) and avoidance (shown in gray) arms. The vertical reference lines indicate where the higher end of the distribution begins to significantly differ ($p < 0.05$) between the randomized arms using bootstrap sampling of 1000 replicates of the upper percentiles. The progressive divergence in the distribution over time demonstrates that very high peanut-specific IgE values are disproportionally represented in the avoidance arm compared to the consumption arm.

Figure S5. Contour Scatter Plots of Peanut-specific IgG4 versus Peanut-specific IgE at 4-11, 12, 30 and 60 Months of Age



Peanut-specific IgG4 is plotted against peanut-specific IgE for individual participants in the peanut avoidance group (top) and the consumption group (bottom). The dark gray to light gray shading represents the density of participants in each part of this distribution. Participants with peanut allergy at 60 months are colored red; non-allergic participants are colored blue.

5. SUPPLEMENTARY TABLES

Table S1. Leap Study Schedule of Events

Age in months	4–10	4–10	4–11	12	13–29	30	31–59	60	
Visit	−1	0	0.01–0.36	12	12.01–12.39	30	30.01–30.30[1]	60	Unscheduled 99
			Weekly phone dietary consultation[2]		Biweekly phone dietary consultation		Monthly phone dietary consultation		USV[3]
Informed consent	X								
Randomization		X							
Dietary education		X	X	X	X	X	X	X	X
General Assessments									
Physical examination	X	X		X		X		X	X
Medical history	X								
Adverse events		X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Dietary history		X	X[4]	X	X[3]	X		X	X
Food reaction history			X	X	X	X	X	X	X
Eczema evaluation	X			X		X		X	
Rhinitis evaluation						X		X	
Asthma evaluation						X		X	
Laboratory Assessments									
Hematology	X							X	
Serum chemistries	X							X	
Skin and nasal swab culture		X		X		X		X	
Allergy Assessments									
SPT for ingested allergens	X			X		X		X	X
SPT for tree nuts								X	
IgE for ingested allergens	X			X		X		X	X
IgE for inhalant allergens						X		X	
Oral food challenges								X	X
Peanut challenges		X						X	X
Peanut Consumption									
Maternal peanut protein consumption history		X							
Participant peanut protein consumption monitoring	X	X	X	X	X	X	X	X	X
Household peanut protein consumption monitoring		X	X[3]	X	X[3]	X		X	X
Immunologic Assessments									
PBMC T-cell assay	X			X		X		X	
Serum allergen-specific immunoglobulins	X			X		X		X	
Serum total IgE	X					X		X	
Plasma allergen archive	X			X		X		X	
Whole blood DNA-HLA genotypes	X			X					

[1] Additional monthly phone dietary consultation visits (30.31 – 30.36) were allowed during the protocol window for V60 i.e. ±6 months

[2] In addition to telephone dietary consultations, an in-home dietary consultation was performed at 9 months of age for participants enrolled younger than 6 months of age and at 21 months of age for all participants.

[3] An unscheduled clinic visit was conducted when necessary for aversion to peanut, refusal of peanut, or both, or for suspected peanut allergy.

[4] Performed only at the in-home dietary consultation.

The Baseline visit occurred between ≥4 to <11 months of age, the V12 visit at 12 months, the V30 visit at 30 months of age and the V60 at 60 months of age; these were face-to-face visits. Visit windows are detailed in Section 6.1 of the Study Protocol (Supplementary Material). Dietary consultations were conducted by telephone and at the above face-to-face visits.

Table S2. Baseline Characteristics

	Negative Stratum (N=542)		Positive Stratum (N=98)		Overall (N=640)	
	Avoidance Group (N=270)	Consumption Group (N=272)	Avoidance Group (N=51)	Consumption Group (N=47)	Avoidance Group (N=321)	Consumption Group (N=319)
Age at screening (mo), mean (SD)	7.7 (1.71)	7.7 (1.77)	8.4 (1.66)	7.9 (1.56)	7.8 (1.72)	7.8 (1.74)
Male sex, no. (%)*	174 (64.4%)	148 (54.4%)	34 (66.7%)	28 (59.6%)	208 (64.8%)	176 (55.2%)
Race, no. (%)						
White	207 (76.7%)	196 (72.1%)	37 (72.5%)	30 (63.8%)	244 (76.0%)	226 (70.8%)
Black	21 (7.8%)	21 (7.7%)	5 (9.8%)	1 (2.1%)	26 (8.1%)	22 (6.9%)
Other						
Mixed	34 (12.6%)	40 (14.7%)	6 (11.8%)	9 (19.1%)	40 (12.5%)	49 (15.4%)
Asian†	6 (2.2%)	10 (3.7%)	3 (5.9%)	5 (10.6%)	9 (2.8%)	15 (4.7%)
Chinese, Middle Eastern or other	2 (0.7%)	4 (1.5%)	0 (0%)	2 (4.3%)	2 (0.6%)	6 (1.9%)
Severe eczema, no. (%)	236 (87.4%)	246 (90.4%)	48 (94.1%)	41 (87.2%)	284 (88.5%)	287 (90.0%)
Age at onset of eczema (mo), mean (SD)	2.2 (1.65)	2.3 (1.61)	2.1 (1.60)	2.4 (1.47)	2.2 (1.64)	2.3 (1.59)
SCORAD, mean (SD)	35.0 (19.87)	33.3 (18.35)	33.7 (16.16)	37.8 (18.64)	34.8 (19.31)	34.0 (18.43)
Total IgE (kU_C/L), mean (SD)	95.1 (321.80)	76.4 (181.39)	125.7 (174.83)	306.4 (666.51)	100.0 (303.24)	109.7 (312.98)
Peanut-specific IgE (kU_A/L), median (IQR)	0.0 (0,0)	0.0 (0,0)	0.4 (0,3)	1.3 (0,5)	0.0 (0,0)	0.0 (0,0)

∗ P-value <0.05 in the overall and in the Negative Stratum comparisons; based on a Fisher's exact test comparing the percentage of subjects in the Avoidance Group to the Consumption Group.
† Participants with origins in the Indian subcontinent.

Table S3. Primary and Secondary Prevention for Different Levels of Sensitization

	Peanut Avoidance (N=313)	Peanut Consumption (N=312)	Total (N=625)	p value
Primary Prevention Group				0.0079[1]
Not Allergic	172 (94.0%)	193 (99.0%)	365 (96.6%)	
Allergic	11 (6.0%)	2 (1.0%)	13 (3.4%)	
Secondary Prevention Group				<0.0001[1]
Not Allergic	87 (66.9%)	109 (93.2%)	196 (79.4%)	
Allergic	43 (33.1%)	8 (6.8%)	51 (20.6%)	
SPT-Negative & IgE Positive				<0.0001[1]
Not Allergic	54 (68.4%)	67 (95.7%)	121 (81.2%)	
Allergic	25 (31.6%)	3 (4.3%)	28 (18.8%)	
SPT-Positive & IgE Positive				0.0061[1]
Not Allergic	22 (59.5%)	34 (87.2%)	56 (73.7%)	
Allergic	15 (40.5%)	5 (12.8%)	20 (26.3%)	
SPT-Positive & IgE Negative				0.1589[1]
Not Allergic	11 (78.6%)	8 (100.0%)	19 (86.4%)	
Allergic	3 (21.4%)	0 (0.0%)	3 (13.6%)	

[1]Chi-Square

The primary prevention group comprised those participants who were both peanut SPT-negative AND specific IgE negative (<0.1 kU_A/L) at baseline, as shown in Table 1. The overall secondary prevention group comprised participants who were either SPT-positive, peanut-specific IgE positive (IgE ≥0.1 kU_A/L), or both at baseline. Table S3 shows the results for the sensitization permutations within the secondary prevention group; these three groups include participants with baseline sensitization results that are SPT Negative AND IgE Positive, SPT Positive AND IgE Positive, and SPT Positive AND IgE Negative. The results demonstrate that the intervention was highly effective in all groups; however, the SPT-Positive AND IgE Negative group included only 22 participants and was not sufficiently powered to detect a statistically significant difference in the prevalence of peanut allergy (21.4% versus 0%, p=0.1589). The sample size for this analysis is 625 (not 628) because of 3 missing peanut specific-IgE values at baseline.

Table S4. Peanut Protein Consumption (grams) by Randomized Group and Stratum

	SPT-negative Stratum		SPT-positive Stratum			
	Peanut Avoidance (N=270)	Peanut Consumption (N=272)	Peanut Avoidance (N=51)	Peanut Consumption (N=47)	Total (N=640)	p value
Average Weekly Consumption First Year of Life						<0.01[1]
Mean (SD)	0.00 (0.00)	6.25 (2.56)	0.00 (0.00)	5.15 (2.65)	3.03 (3.55)	
Median	0.00	6.38	0.00	6.00	0.00	
Range	(0.00-0.04)	(0.00-14.29)	(0.00-0.00)	(0.00-8.84)	(0.00-14.29)	
Average Weekly Consumption Second Year of Life[2]						<0.01[1]
Mean (SD)	0.02 (0.18)	8.44 (2.81)	0.00 (0.01)	7.20 (3.69)	4.13 (4.63)	
Median	0.00	8.37	0.00	8.23	0.01	
Range	(0.00-2.75)	(0.00-18.09)	(0.00-0.07)	(0.00-13.69)	(0.00-18.09)	
Average Weekly Consumption First and Second Years of Life						<0.01[1]
Mean (SD)	0.01 (0.10)	7.76 (2.30)	0.00 (0.01)	6.58 (3.30)	3.79 (4.18)	
Median	0.00	7.69	0.00	7.45	0.02	
Range	(0.00-1.55)	(0.00-15.17)	(0.00-0.04)	(0.00-11.64)	(0.00-15.17)	

[1]Kruskal Wallis

[2]Three participants in the SPT-negative Stratum (2 in avoidance and 1 in consumption) were missing weekly consumption data during the second year of life.

Peanut protein consumption (in grams) in the first two years of life as measured by a validated food frequency questionnaire administered during telephone and clinic visits.

Table S5. Peanut Protein in Bed Dust at 60 Months of Age by Stratum

	Peanut Protein in Dust by Stratum			
	SPT-negative Stratum (N=355)	SPT-positive Stratum (N=68)	Total (N=423)	p value
Peanut Protein in Dust (mcg/gram dust)				0.70[1]
N	350	67	417	
Median	18.0	18.3	18.1	
Range	(0.2-4140.6)	(0.2-1165.2)	(0.2-4140.6)	

[1]Wilcoxon

Table S6. All Cause Hospitalizations and Mortality

All Cause Hospitalizations and Mortality				
	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p value
Number of Hospitalizations				0.83[1]
0	269 (83.8%)	269 (84.3%)	538 (84.1%)	
1	37 (11.5%)	36 (11.3%)	73 (11.4%)	
2	10 (3.1%)	11 (3.4%)	21 (3.3%)	
3	3 (0.9%)	2 (0.6%)	5 (0.8%)	
4	2 (0.6%)	0 (0.0%)	2 (0.3%)	
5	0 (0.0%)	1 (0.3%)	1 (0.2%)	
Was Subject Ever Hospitalized?				0.86[2]
No	269 (83.8%)	269 (84.3%)	538 (84.1%)	
Yes	52 (16.2%)	50 (15.7%)	102 (15.9%)	
Did Subject Die?				
No	321 (100.0%)	319 (100.0%)	640 (100.0%)	

[1]Fisher Exact [2]Chi-Square

Table S7. Serious Adverse Events

	Negative Stratum (N=542)		Positive Stratum (N=98)		Overall (N=640)				
	Avoidance Group (N=270)	Consumption Group (N=272)	Avoidance Group (N=51)	Consumption Group (N=47)	Avoidance Group (N=321)	Consumption Group (N=319)	P-value [1] SPT-Neg	P-value [2] SPT-Pos	P-value [3] Overall
Number of Events	78	65	23	24	101	89			
Number of Participants with at Least One Event	55(20.4)	47(17.3)	15(29.4)	14(29.8)	70(21.8)	61(19.1)	0.380	>0.999	0.434
Respiratory, thoracic and mediastinal disorders	19(7.0)	24(8.8)	8(15.7)	9(19.1)	27(8.4)	33(10.3)	0.526	0.791	0.419
Wheezing	17(6.3)	18(6.6)	6(11.8)	6(12.8)	23(7.2)	24(7.5)	>0.999	>0.999	0.881
Asthma	4(1.5)	9(3.3)	2(3.9)	2(4.3)	6(1.9)	11(3.4)	0.261	>0.999	0.230
Lung consolidation	0(0)	0(0)	0(0)	1(2.1)	0(0)	1(0.3)		0.480	0.498
Respiratory failure	0(0)	0(0)	0(0)	1(2.1)	0(0)	1(0.3)		0.480	0.498
Infections and infestations	24(8.9)	15(5.5)	2(3.9)	4(8.5)	26(8.1)	19(6.0)	0.138	0.423	0.354
Gastroenteritis	4(1.5)	3(1.1)	1(2.0)	1(2.1)	5(1.6)	4(1.3)	0.724	>0.999	>0.999
Pneumonia	3(1.1)	2(0.7)	0(0)	0(0)	3(0.9)	2(0.6)	0.685		>0.999
Gastroenteritis viral	1(0.4)	3(1.1)	0(0)	0(0)	1(0.3)	3(0.9)	0.624		0.372
Viral infection	4(1.5)	0(0)	0(0)	0(0)	4(1.2)	0(0)	0.061		0.124
Eczema herpeticum	0(0)	1(0.4)	1(2.0)	1(2.1)	1(0.3)	2(0.6)	>0.999	>0.999	0.623
Eczema infected	1(0.4)	2(0.7)	0(0)	0(0)	1(0.3)	2(0.6)	>0.999		0.623
Cellulitis	2(0.7)	0(0)	0(0)	0(0)	2(0.6)	0(0)	0.248		0.499
Lower respiratory tract infection	1(0.4)	0(0)	0(0)	1(2.1)	1(0.3)	1(0.3)	0.498	0.480	>0.999
Tonsillitis	1(0.4)	1(0.4)	0(0)	0(0)	1(0.3)	1(0.3)	>0.999		>0.999
Upper respiratory tract infection	2(0.7)	0(0)	0(0)	0(0)	2(0.6)	0(0)	0.248		0.499
Urinary tract infection	1(0.4)	1(0.4)	0(0)	0(0)	1(0.3)	1(0.3)	>0.999		>0.999
Arthritis bacterial	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	>0.999		0.498

Note: At each level of summarization, a participant is counted once if the participant reported one or more events. Events are coded according to MedDRA V11.1.

[1] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-negative stratum.

[2] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-positive stratum.

[3] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group across both the SPT-negative and SPT-positive strata.

All AE and SAE data are also available in an interactive explorer at http://graphics.rhoworld.com/studies/leap/aes/explorer/.

	Negative Stratum (N=542)		Positive Stratum (N=98)		Overall (N=640)		P-value [1]	P-value [2]	P-value [3]
	Avoidance Group (N=270)	Consumption Group (N=272)	Avoidance Group (N=51)	Consumption Group (N=47)	Avoidance Group (N=321)	Consumption Group (N=319)	SPT-Neg	SPT-Pos	Overall
Infections and infestations									
Bronchiolitis	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Febrile infection	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	>0.999		0.498
Measles	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Meningitis viral	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Meningococcal sepsis	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Paronychia	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Sepsis	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Urinary tract infection pseudomonal	0(0)	0(0)	0(0)	1(2.1)	0(0)	1(0.3)		0.480	0.498
Varicella	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Viral tonsillitis	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	>0.999		0.498
Immune system disorders	7(2.6)	2(0.7)	7(13.7)	4(8.5)	14(4.4)	6(1.9)	0.105	0.528	0.110
Anaphylactic reaction	5(1.9)	0(0)	7(13.7)	3(6.4)	12(3.7)	3(0.9)	0.030	0.322	0.033
Food allergy	0(0)	2(0.7)	0(0)	2(4.3)	0(0)	4(1.3)	0.499	0.227	0.061
Allergy to animal	0(0)	0(0)	1(2.0)	0(0)	1(0.3)	0(0)		>0.999	>0.999
Hypersensitivity	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Milk allergy	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Injury, poisoning and procedural complications	5(1.9)	4(1.5)	1(2.0)	1(2.1)	6(1.9)	5(1.6)	0.751	>0.999	>0.999
Head injury	2(0.7)	2(0.7)	0(0)	0(0)	2(0.6)	2(0.6)	>0.999		>0.999
Forearm fracture	0(0)	1(0.4)	0(0)	1(2.1)	0(0)	2(0.6)	>0.999	0.480	0.248
Foreign body trauma	1(0.4)	0(0)	1(2.0)	0(0)	2(0.6)	0(0)	0.498	>0.999	0.499
Post procedural haemorrhage	2(0.7)	0(0)	0(0)	0(0)	2(0.6)	0(0)	0.248		0.499

Note: At each level of summarization, a participant is counted once if the participant reported one or more events. Events are coded according to MedDRA V11.1.

[1] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-negative stratum.

[2] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-positive stratum.

[3] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group across both the SPT-negative and SPT-positive strata.

	Negative Stratum (N=542)		Positive Stratum (N=98)		Overall (N=640)				
	Avoidance Group (N=270)	Consumption Group (N=272)	Avoidance Group (N=51)	Consumption Group (N=47)	Avoidance Group (N=321)	Consumption Group (N=319)	P-value [1] SPT-Neg	P-value [2] SPT-Pos	P-value [3] Overall
Injury, poisoning and procedural complications									
Clavicle fracture	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	>0.999		0.498
Nervous system disorders	2(0.7)	4(1.5)	0(0)	0(0)	2(0.6)	4(1.3)	0.686		0.450
Febrile convulsion	2(0.7)	4(1.5)	0(0)	0(0)	2(0.6)	4(1.3)	0.686		0.450
Gastrointestinal disorders	1(0.4)	1(0.4)	0(0)	0(0)	1(0.3)	1(0.3)	>0.999		>0.999
Inguinal hernia strangulated	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	>0.999		0.498
Intussusception	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Skin and subcutaneous tissue disorders	0(0)	2(0.7)	0(0)	0(0)	0(0)	2(0.6)	0.499		0.248
Swelling face	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	>0.999		0.498
Urticaria	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	>0.999		0.498
General disorders and administration site conditions	0(0)	0(0)	1(2.0)	0(0)	1(0.3)	0(0)		>0.999	>0.999
Pyrexia	0(0)	0(0)	1(2.0)	0(0)	1(0.3)	0(0)		>0.999	>0.999
Hepatobiliary disorders	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Hepatitis	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Metabolism and nutrition disorders	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Diabetes mellitus	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Diabetic ketoacidosis	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999

Note: At each level of summarization, a participant is counted once if the participant reported one or more events. Events are coded according to MedDRA V11.1.

[1] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-negative stratum.

[2] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-positive stratum.

[3] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group across both the SPT-negative and SPT-positive strata.

	Negative Stratum (N=542)		Positive Stratum (N=98)		Overall (N=640)				
	Avoidance Group (N=270)	Consumption Group (N=272)	Avoidance Group (N=51)	Consumption Group (N=47)	Avoidance Group (N=321)	Consumption Group (N=319)	P-value [1] SPT-Neg	P-value [2] SPT-Pos	P-value [3] Overall
Musculoskeletal and connective tissue disorders	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999
Arthritis reactive	1(0.4)	0(0)	0(0)	0(0)	1(0.3)	0(0)	0.498		>0.999

Note: At each level of summarization, a participant is counted once if the participant reported one or more events. Events are coded according to MedDRA V11.1.

[1] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-negative stratum.

[2] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group within the SPT-positive stratum.

[3] P-value is from a Fisher's exact test comparing the percentage of subjects with an SAE in the Peanut Avoidance Group to the Peanut Consumption Group across both the SPT-negative and SPT-positive strata.

Table S8. Adverse Events - Poisson Analysis

System Organ Class Preferred Term	Peanut Avoidance (N=321) No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	Peanut Consumption (N=319) No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	Rel. Risk [3]	Subject Level p-value [1]	Rate Ratio [3]	Event Level p-value [2]
Any AE	319	(99.4%)	4287	3.022	318	(99.7%)	4527	3.179	0.997	0.446	0.950	0.017
Infections and infestations	318	(99.1%)	2128	1.500	317	(99.4%)	2358	1.656	0.997	0.490	0.906	<.001
Upper respiratory tract infection	187	(58.3%)	337	0.238	222	(69.6%)	470	0.330	0.837	0.005	0.720	<.001
Gastroenteritis	170	(53.0%)	276	0.195	203	(63.6%)	349	0.245	0.832	0.010	0.794	0.004
Rhinitis	184	(57.3%)	206	0.145	177	(55.5%)	204	0.143	1.033	0.543	1.013	0.892
Varicella	143	(44.5%)	146	0.103	162	(50.8%)	170	0.119	0.877	0.145	0.862	0.187
Lower respiratory tract infection	117	(36.4%)	198	0.140	103	(32.3%)	165	0.116	1.129	0.231	1.204	0.077
Ear infection	94	(29.3%)	157	0.111	100	(31.3%)	158	0.111	0.934	0.628	0.997	0.981
Nasopharyngitis	89	(27.7%)	107	0.075	101	(31.7%)	132	0.093	0.876	0.314	0.814	0.112
Viral infection	52	(16.2%)	60	0.042	66	(20.7%)	81	0.057	0.783	0.159	0.743	0.080
Tonsillitis	55	(17.1%)	79	0.056	62	(19.4%)	99	0.070	0.882	0.488	0.801	0.140
Eczema infected	46	(14.3%)	63	0.044	29	(9.1%)	48	0.034	1.576	0.035	1.317	0.148
Otitis media	39	(12.1%)	47	0.033	31	(9.7%)	34	0.024	1.250	0.304	1.387	0.143
Viral skin infection	23	(7.2%)	24	0.017	47	(14.7%)	50	0.035	0.486	0.002	0.482	0.002
Viral upper respiratory tract infection	34	(10.6%)	39	0.027	36	(11.3%)	41	0.029	0.939	0.812	0.955	0.836
Croup infectious	35	(10.9%)	39	0.027	25	(7.8%)	32	0.022	1.391	0.171	1.223	0.397
Respiratory tract infection	24	(7.5%)	27	0.019	29	(9.1%)	32	0.022	0.822	0.481	0.847	0.524
Molluscum contagiosum	24	(7.5%)	26	0.018	25	(7.8%)	27	0.019	0.954	0.892	0.966	0.901
Pharyngitis	25	(7.8%)	30	0.021	17	(5.3%)	19	0.013	1.461	0.197	1.585	0.112
Urinary tract infection	22	(6.9%)	27	0.019	17	(5.3%)	28	0.020	1.286	0.402	0.968	0.903
Impetigo	18	(5.6%)	33	0.023	20	(6.3%)	26	0.018	0.894	0.747	1.274	0.354
Influenza	14	(4.4%)	15	0.011	21	(6.6%)	22	0.015	0.663	0.228	0.684	0.253
Eye infection	19	(5.9%)	21	0.015	13	(4.1%)	15	0.011	1.452	0.272	1.405	0.311
Hand-foot-and-mouth disease	11	(3.4%)	11	0.008	15	(4.7%)	17	0.012	0.729	0.429	0.649	0.259
Bronchiolitis	9	(2.8%)	10	0.007	15	(4.7%)	18	0.013	0.596	0.215	0.558	0.130
Skin infection	15	(4.7%)	16	0.011	9	(2.8%)	9	0.006	1.656	0.209	1.784	0.156

[1] The subject-level p-value comes from a ln-Poisson regression model as described in Zou (J Epidemiol 2004; 159;702-6). The comparison is adjusted for the ln follow-up time contributed by each subject.

[2] The event level p-value comes from a poisson regression comparing the person-year adjusted event rates between the two treatment groups.

[3] Relative risks (and Rate Ratios) are calculated as Peanut Avoidance (Rate) divided by Peanut Consumption (Rate).

Preferred terms highlighted in gray are those with a p-value < .01 using either method. Relative Risks and Incidence Ratios cannot be computed for preferred terms where the event count is zero in either treatment group.

Only preferred terms with 5 or more events are included in the table.

System Organ Class Preferred Term	Peanut Avoidance (N=321) No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	Peanut Consumption (N=319) No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	Rel. Risk [3]	Subject Level p-value [1]	Rate Ratio [3]	Event Level p-value [2]
Infections and infestations												
Herpes zoster	7	(2.2%)	7	0.005	13	(4.1%)	13	0.009	0.535	0.175	0.540	0.179
Gastroenteritis viral	7	(2.2%)	7	0.005	8	(2.5%)	9	0.006	0.870	0.799	0.781	0.622
Candidiasis	4	(1.2%)	4	0.003	5	(1.6%)	5	0.004	0.795	0.741	0.803	0.743
Cellulitis	6	(1.9%)	7	0.005	2	(0.6%)	2	0.001	2.981	0.153	3.513	0.085
Fungal infection	3	(0.9%)	3	0.002	5	(1.6%)	6	0.004	0.596	0.480	0.502	0.315
Oral candidiasis	6	(1.9%)	6	0.004	2	(0.6%)	2	0.001	2.981	0.154	3.011	0.147
Paronychia	8	(2.5%)	9	0.006	0	(0)	0			0.004		<.001
Tinea infection	6	(1.9%)	8	0.006	2	(0.6%)	2	0.001	2.981	0.154	4.014	0.049
Measles	5	(1.6%)	5	0.004	2	(0.6%)	2	0.001	2.484	0.252	2.509	0.247
Pneumonia	4	(1.2%)	6	0.004	3	(0.9%)	3	0.002	1.325	0.700	2.007	0.310
Scarlet fever	4	(1.2%)	4	0.003	3	(0.9%)	3	0.002	1.325	0.701	1.338	0.701
Erythema infectiosum	1	(0.3%)	1	0.001	5	(1.6%)	5	0.004	0.199	0.101	0.201	0.089
Fungal skin infection	2	(0.6%)	2	0.001	3	(0.9%)	4	0.003	0.663	0.656	0.502	0.412
Lower respiratory tract infection viral	5	(1.6%)	5	0.004	0	(0)	0			0.025		0.008
Genital infection	3	(0.9%)	3	0.002	1	(0.3%)	2	0.001	2.981	0.315	1.505	0.651
Helminthic infection	2	(0.6%)	2	0.001	2	(0.6%)	3	0.002	0.994	0.997	0.669	0.657
Skin and subcutaneous tissue disorders	211	(65.7%)	480	0.338	234	(73.4%)	517	0.363	0.896	0.060	0.932	0.265
Eczema	162	(50.5%)	293	0.207	174	(54.5%)	300	0.211	0.925	0.370	0.980	0.808
Urticaria	40	(12.5%)	66	0.047	72	(22.6%)	102	0.072	0.552	<.001	0.649	0.006
Rash	45	(14.0%)	54	0.038	38	(11.9%)	46	0.032	1.177	0.400	1.178	0.413
Dermatitis diaper	17	(5.3%)	17	0.012	9	(2.8%)	10	0.007	1.877	0.107	1.706	0.173
Angioedema	6	(1.9%)	6	0.004	13	(4.1%)	18	0.013	0.459	0.105	0.335	0.013
Dermatitis contact	8	(2.5%)	10	0.007	8	(2.5%)	10	0.007	0.994	0.994	1.004	0.994
Keratosis pilaris	6	(1.9%)	7	0.005	3	(0.9%)	3	0.002	1.988	0.312	2.342	0.198
Rash maculo-papular	3	(0.9%)	3	0.002	3	(0.9%)	3	0.002	0.994	0.996	1.004	0.996
Dermatitis allergic	5	(1.6%)	5	0.004	0	(0)	0			0.025		0.008

[1] The subject-level p-value comes from a ln-Poisson regression model as described in Zou (J Epidemiol 2004; 159;702-6). The comparison is adjusted for the ln follow-up time contributed by each subject.

[2] The event level p-value comes from a poisson regression comparing the person-year adjusted event rates between the two treatment groups.

[3] Relative risks (and Rate Ratios) are calculated as Peanut Avoidance (Rate) divided by Peanut Consumption (Rate).

Preferred terms highlighted in gray are those with a p-value < .01 using either method. Relative Risks and Incidence Ratios cannot be computed for preferred terms where the event count is zero in either treatment group.

Only preferred terms with 5 or more events are included in the table.

System Organ Class Preferred Term	Peanut Avoidance (N=321) No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	Peanut Consumption (N=319) No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	Rel. Risk [3]	Subject Level p-value [1]	Rate Ratio [3]	Event Level p-value [2]
Skin and subcutaneous tissue disorders												
Rash macular	1	(0.3%)	1	0.001	4	(1.3%)	4	0.003	0.248	0.179	0.251	0.166
Immune system disorders	201	(62.6%)	635	0.448	199	(62.4%)	584	0.410	1.004	0.824	1.091	0.128
Food allergy	163	(50.8%)	397	0.280	162	(50.8%)	386	0.271	1.000	0.900	1.032	0.657
Seasonal allergy	47	(14.6%)	58	0.041	40	(12.5%)	48	0.034	1.168	0.409	1.213	0.322
Milk allergy	47	(14.6%)	93	0.066	38	(11.9%)	68	0.048	1.229	0.287	1.373	0.046
Hypersensitivity	18	(5.6%)	22	0.016	24	(7.5%)	26	0.018	0.745	0.344	0.849	0.572
Allergy to animal	14	(4.4%)	16	0.011	18	(5.6%)	21	0.015	0.773	0.474	0.765	0.417
Drug hypersensitivity	14	(4.4%)	15	0.011	11	(3.4%)	11	0.008	1.265	0.535	1.369	0.426
Anaphylactic reaction	13	(4.0%)	15	0.011	3	(0.9%)	5	0.004	4.306	0.011	3.011	0.022
Allergy to vaccine	10	(3.1%)	10	0.007	4	(1.3%)	4	0.003	2.484	0.104	2.509	0.102
Oral allergy syndrome	2	(0.6%)	3	0.002	2	(0.6%)	2	0.001	0.994	0.997	1.505	0.651
House dust allergy	1	(0.3%)	1	0.001	2	(0.6%)	4	0.003	0.497	0.565	0.251	0.166
Respiratory, thoracic and mediastinal disorders	159	(49.5%)	401	0.283	152	(47.6%)	439	0.308	1.040	0.550	0.917	0.208
Wheezing	89	(27.7%)	187	0.132	79	(24.8%)	173	0.121	1.120	0.355	1.085	0.440
Asthma	76	(23.7%)	113	0.080	85	(26.6%)	163	0.114	0.889	0.427	0.696	0.003
Cough	68	(21.2%)	83	0.059	63	(19.7%)	77	0.054	1.073	0.609	1.082	0.619
Rhinitis seasonal	4	(1.2%)	4	0.003	10	(3.1%)	12	0.008	0.398	0.106	0.335	0.041
Epistaxis	2	(0.6%)	2	0.001	6	(1.9%)	6	0.004	0.331	0.156	0.335	0.149
Gastrointestinal disorders	149	(46.4%)	238	0.168	156	(48.9%)	267	0.188	0.949	0.609	0.895	0.211
Vomiting	72	(22.4%)	92	0.065	79	(24.8%)	109	0.077	0.906	0.531	0.847	0.240
Diarrhoea	72	(22.4%)	78	0.055	67	(21.0%)	89	0.063	1.068	0.614	0.880	0.408
Constipation	27	(8.4%)	35	0.025	32	(10.0%)	38	0.027	0.838	0.503	0.924	0.737
Abdominal pain	6	(1.9%)	6	0.004	10	(3.1%)	12	0.008	0.596	0.314	0.502	0.156

[1] The subject-level p-value comes from a ln-Poisson regression model as described in Zou (J Epidemiol 2004; 159;702-6). The comparison is adjusted for the ln follow-up time contributed by each subject.
[2] The event level p-value comes from a poisson regression comparing the person-year adjusted event rates between the two treatment groups.
[3] Relative risks (and Rate Ratios) are calculated as Peanut Avoidance (Rate) divided by Peanut Consumption (Rate).
Preferred terms highlighted in gray are those with a p-value < .01 using either method. Relative Risks and Incidence Ratios cannot be computed for preferred terms where the event count is zero in either treatment group.
Only preferred terms with 5 or more events are included in the table.

System Organ Class Preferred Term	Peanut Avoidance (N=321) No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	Peanut Consumption (N=319) No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	Rel. Risk [3]	Subject Level p-value [1]	Rate Ratio [3]	Event Level p-value [2]
Gastrointestinal disorders												
Gastrooesophageal reflux disease	9	(2.8%)	10	0.007	5	(1.6%)	6	0.004	1.789	0.277	1.673	0.311
General disorders and administration site conditions	93	(29.0%)	129	0.091	108	(33.9%)	138	0.097	0.856	0.211	0.938	0.602
Pyrexia	81	(25.2%)	111	0.078	98	(30.7%)	122	0.086	0.821	0.141	0.913	0.488
Influenza like illness	9	(2.8%)	9	0.006	10	(3.1%)	10	0.007	0.894	0.822	0.903	0.825
Eye disorders	94	(29.3%)	111	0.078	73	(22.9%)	80	0.056	1.280	0.055	1.393	0.023
Conjunctivitis	81	(25.2%)	97	0.068	53	(16.6%)	56	0.039	1.519	0.006	1.738	<.001
Conjunctivitis allergic	1	(0.3%)	1	0.001	5	(1.6%)	5	0.004	0.199	0.101	0.201	0.089
Astigmatism	3	(0.9%)	3	0.002	2	(0.6%)	2	0.001	1.491	0.651	1.505	0.651
Myopia	1	(0.3%)	1	0.001	4	(1.3%)	4	0.003	0.248	0.179	0.251	0.166
Injury, poisoning and procedural complications	52	(16.2%)	64	0.045	50	(15.7%)	61	0.043	1.034	0.813	1.053	0.773
Head injury	15	(4.7%)	17	0.012	12	(3.8%)	13	0.009	1.242	0.549	1.312	0.459
Limb injury	6	(1.9%)	6	0.004	6	(1.9%)	6	0.004	0.994	0.995	1.004	0.995
Thermal burn	2	(0.6%)	2	0.001	5	(1.6%)	5	0.004	0.398	0.256	0.401	0.251
Clavicle fracture	1	(0.3%)	1	0.001	4	(1.3%)	4	0.003	0.248	0.179	0.251	0.166
Joint injury	5	(1.6%)	6	0.004	0	(0)	0			0.025		0.004
Mouth injury	2	(0.6%)	2	0.001	3	(0.9%)	3	0.002	0.663	0.656	0.669	0.657
Metabolism and nutrition disorders	30	(9.3%)	34	0.024	22	(6.9%)	23	0.016	1.355	0.241	1.484	0.140
Obesity	14	(4.4%)	14	0.010	8	(2.5%)	8	0.006	1.739	0.190	1.756	0.195
Failure to thrive	7	(2.2%)	7	0.005	6	(1.9%)	6	0.004	1.159	0.774	1.171	0.776

[1] The subject-level p-value comes from a ln-Poisson regression model as described in Zou (J Epidemiol 2004; 159;702-6). The comparison is adjusted for the ln follow-up time contributed by each subject.
[2] The event level p-value comes from a poisson regression comparing the person-year adjusted event rates between the two treatment groups.
[3] Relative risks (and Rate Ratios) are calculated as Peanut Avoidance (Rate) divided by Peanut Consumption (Rate).
Preferred terms highlighted in gray are those with a p-value < .01 using either method. Relative Risks and Incidence Ratios cannot be computed for preferred terms where the event count is zero in either treatment group.
Only preferred terms with 5 or more events are included in the table.

System Organ Class Preferred Term	Peanut Avoidance (N=321) No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	Peanut Consumption (N=319) No. Pts with >=1 AE	Pct. Pts	No. Events	Event Rate	Rel. Risk [3]	Subject Level p-value [1]	Rate Ratio [3]	Event Level p-value [2]
Nervous system disorders	9	(2.8%)	11	0.008	13	(4.1%)	16	0.011	0.688	0.390	0.690	0.339
Febrile convulsion	3	(0.9%)	4	0.003	5	(1.6%)	7	0.005	0.596	0.480	0.573	0.366
Musculoskeletal and connective tissue disorders	13	(4.0%)	15	0.011	7	(2.2%)	7	0.005	1.846	0.171	2.151	0.083
Ear and labyrinth disorders	12	(3.7%)	12	0.008	5	(1.6%)	5	0.004	2.385	0.084	2.409	0.084
Ear pain	4	(1.2%)	4	0.003	1	(0.3%)	1	0.001	3.975	0.177	4.014	0.164
Tympanic membrane perforation	4	(1.2%)	4	0.003	1	(0.3%)	1	0.001	3.975	0.177	4.014	0.164
Blood and lymphatic system disorders	8	(2.5%)	10	0.007	8	(2.5%)	9	0.006	0.994	0.994	1.115	0.812
Anaemia	3	(0.9%)	3	0.002	3	(0.9%)	3	0.002	0.994	0.996	1.004	0.996
Lymphadenitis	4	(1.2%)	5	0.004	2	(0.6%)	2	0.001	1.988	0.410	2.509	0.247
Lymphadenopathy	2	(0.6%)	2	0.001	3	(0.9%)	3	0.002	0.663	0.656	0.669	0.657
Congenital, familial and genetic disorders	6	(1.9%)	6	0.004	5	(1.6%)	5	0.004	1.193	0.757	1.204	0.758
Psychiatric disorders	6	(1.9%)	6	0.004	5	(1.6%)	5	0.004	1.193	0.757	1.204	0.758

[1] The subject-level p-value comes from a ln-Poisson regression model as described in Zou (J Epidemiol 2004; 159;702-6). The comparison is adjusted for the ln follow-up time contributed by each subject.
[2] The event level p-value comes from a poisson regression comparing the person-year adjusted event rates between the two treatment groups.
[3] Relative risks (and Rate Ratios) are calculated as Peanut Avoidance (Rate) divided by Peanut Consumption (Rate).
Preferred terms highlighted in gray are those with a p-value < .01 using either method. Relative Risks and Incidence Ratios cannot be computed for preferred terms where the event count is zero in either treatment group.
Only preferred terms with 5 or more events are included in the table.

Table S9. Adverse Events of Interest

Table S9a. Adverse Events of Interest - Upper Respiratory Tract Infection

	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p-value
Severity of Upper Respiratory Tract Infection Events				0.416[1]
Mild	139(43.3%)	157(49.2%)	296(46.3%)	
Moderate	48(15.0%)	65(20.4%)	113(17.7%)	
Baseline Peanut-specific IgE Category[2]				0.517[1]
Above 0.1	68(21.2%)	74(23.2%)	142(22.2%)	
Below 0.1	118(36.8%)	147(46.1%)	265(41.4%)	
Stratum				0.986[1]
SPT-negative Stratum	161(50.2%)	191(59.9%)	352(55.0%)	
SPT-positive Stratum	26(8.1%)	31(9.7%)	57(8.9%)	
Total Number of Upper Respiratory Tract Infection Events				<0.001[3]
0	134(41.7%)	97(30.4%)	231(36.1%)	
1	96(29.9%)	99(31.0%)	195(30.5%)	
2	54(16.8%)	55(17.2%)	109(17.0%)	
3	23(7.2%)	40(12.5%)	63(9.8%)	
4	7(2.2%)	13(4.1%)	20(3.1%)	
5	6(1.9%)	7(2.2%)	13(2.0%)	
6	1(0.3%)	5(1.6%)	6(0.9%)	
7	0(0%)	2(0.6%)	2(0.3%)	
10	0(0%)	1(0.3%)	1(0.2%)	

[1]Chi-Square
[2]At baseline, one participant in each group was missing IgE data.
[3]Wilcoxon Rank Sum

Table S9b. Adverse Events of Interest - Viral Skin Infection

	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p-value
Severity of Viral Skin Infection Events				0.007[1]
Mild	17(5.3%)	45(14.1%)	62(9.7%)	
Moderate	6(1.9%)	2(0.6%)	8(1.3%)	
Baseline Peanut-specific IgE Category[2]				>0.999[1]
Above 0.1	6(1.9%)	12(3.8%)	18(2.8%)	
Below 0.1	17(5.3%)	34(10.7%)	51(8.0%)	
Stratum				0.615[1]
SPT-negative Stratum	21(6.5%)	41(12.9%)	62(9.7%)	
SPT-positive Stratum	2(0.6%)	6(1.9%)	8(1.3%)	
Total Number of Viral Skin Infection Events				0.002[3]
0	298(92.8%)	272(85.3%)	570(89.1%)	
1	22(6.9%)	44(13.8%)	66(10.3%)	
2	1(0.3%)	3(0.9%)	4(0.6%)	

[1]Chi-Square
[2]At baseline, one participant in each group was missing IgE data.
[3]Wilcoxon Rank Sum

Table S9c. Adverse Events of Interest - Asthma

	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p-value
Severity of Asthma Events				0.839[1]
Mild	1(0.3%)	2(0.6%)	3(0.5%)	
Moderate	73(22.7%)	80(25.1%)	153(23.9%)	
Severe	2(0.6%)	3(0.9%)	5(0.8%)	
Baseline Peanut-specific IgE Category[2]				0.544[1]
Above 0.1	34(10.6%)	34(10.7%)	68(10.6%)	
Below 0.1	42(13.1%)	51(16.0%)	93(14.5%)	
Stratum				0.869[1]
SPT-negative Stratum	60(18.7%)	68(21.3%)	128(20.0%)	
SPT-positive Stratum	16(5.0%)	17(5.3%)	33(5.2%)	
Total Number of Asthma Events				0.292[3]
0	245(76.3%)	234(73.4%)	479(74.8%)	
1	51(15.9%)	50(15.7%)	101(15.8%)	
2	19(5.9%)	20(6.3%)	39(6.1%)	
3	1(0.3%)	6(1.9%)	7(1.1%)	
4	4(1.2%)	4(1.3%)	8(1.3%)	
5	1(0.3%)	0(0%)	1(0.2%)	
7	0(0%)	2(0.6%)	2(0.3%)	
8	0(0%)	2(0.6%)	2(0.3%)	
9	0(0%)	1(0.3%)	1(0.2%)	

[1]Chi-Square
[2]At baseline, one participant in each group was missing IgE data.
[3]Wilcoxon Rank Sum

Table S9d. Adverse Events of Interest - Gastroenteritis

	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p-value
Severity of Gastroenteritis Events				0.401[1]
Mild	134(41.7%)	171(53.6%)	305(47.7%)	
Moderate	35(10.9%)	31(9.7%)	66(10.3%)	
Severe	1(0.3%)	1(0.3%)	2(0.3%)	
Baseline Peanut-specific IgE Category[2]				0.096[1]
Above 0.1	67(20.9%)	63(19.7%)	130(20.3%)	
Below 0.1	102(31.8%)	138(43.3%)	240(37.5%)	
Stratum				0.306[1]
SPT-negative Stratum	140(43.6%)	175(54.9%)	315(49.2%)	
SPT-positive Stratum	30(9.3%)	28(8.8%)	58(9.1%)	
Total Number of Gastroenteritis Events				0.007[3]
0	151(47.0%)	116(36.4%)	267(41.7%)	
1	100(31.2%)	118(37.0%)	218(34.1%)	
2	44(13.7%)	43(13.5%)	87(13.6%)	
3	18(5.6%)	27(8.5%)	45(7.0%)	
4	6(1.9%)	11(3.4%)	17(2.7%)	
5	2(0.6%)	4(1.3%)	6(0.9%)	

[1]Chi-Square
[2]At baseline, one participant in each group was missing IgE data.
[3]Wilcoxon Rank Sum

Table S9e. Adverse Events of Interest - Urticaria

	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p-value
Severity of Urticaria Events				0.222[1]
Mild	12(3.7%)	30(9.4%)	42(6.6%)	
Moderate	28(8.7%)	42(13.2%)	70(10.9%)	
Baseline Peanut-specific IgE Category[2]				0.298[1]
Above 0.1	21(6.5%)	30(9.4%)	51(8.0%)	
Below 0.1	19(5.9%)	41(12.9%)	60(9.4%)	
Stratum				0.894[1]
SPT-negative Stratum	31(9.7%)	55(17.2%)	86(13.4%)	
SPT-positive Stratum	9(2.8%)	17(5.3%)	26(4.1%)	
Total Number of Urticaria Events				0.001[3]
0	281(87.5%)	247(77.4%)	528(82.5%)	
1	22(6.9%)	50(15.7%)	72(11.3%)	
2	14(4.4%)	16(5.0%)	30(4.7%)	
3	1(0.3%)	4(1.3%)	5(0.8%)	
4	2(0.6%)	2(0.6%)	4(0.6%)	
5	1(0.3%)	0(0%)	1(0.2%)	

[1]Chi-Square
[2]At baseline, one participant in each group was missing IgE data.
[3]Wilcoxon Rank Sum

Table S9f. Adverse Events of Interest - Conjunctivitis

	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p-value
Severity of Conjunctivitis Events				0.613[1]
Mild	50(15.6%)	35(11.0%)	85(13.3%)	
Moderate	31(9.7%)	18(5.6%)	49(7.7%)	
Baseline Peanut-specific IgE Category[2]				0.787[1]
Above 0.1	29(9.0%)	18(5.6%)	47(7.3%)	
Below 0.1	51(15.9%)	35(11.0%)	86(13.4%)	
Stratum				0.806[1]
SPT-negative Stratum	70(21.8%)	45(14.1%)	115(18.0%)	
SPT-positive Stratum	11(3.4%)	8(2.5%)	19(3.0%)	
Total Number of Conjunctivitis Events				0.004[3]
0	240(74.8%)	266(83.4%)	506(79.1%)	
1	65(20.2%)	51(16.0%)	116(18.1%)	
2	16(5.0%)	1(0.3%)	17(2.7%)	
3	0(0%)	1(0.3%)	1(0.2%)	

[1]Chi-Square
[2]At baseline, one participant in each group was missing IgE data.
[3]Wilcoxon Rank Sum

Table S10. Participants Who Discontinued Peanut Consumption

Stratum[1]	Age of peanut discontinuation	Sequence of medical events, prior to discontinuation.	Peanut-induced allergic symptoms as reason for discontinuation	V60 peanut OFC[2] outcome
1. SPT-Negative Stratum i.e. SPT to peanut 0 mm at baseline.	19 months	Parental caution to feed peanut as per study protocol. Participant developed active dislike of peanut, and then stopped eating peanut. SPT at most recent visit (12 months of age) was 0 mm.	No	Positive
2.SPT-Negative Stratum	39 months (Participant met per-protocol definition)	Peanut-induced facial hives; peanut had been eaten prior to that event. Peanut ingestion stopped. SPT at most recent visit (30 months of age) was 5 mm. Baseline OFC had resulted in a single hive but repeat baseline challenge was negative.	Yes	Positive
3. SPT-Negative Stratum	28 months	Peanut-induced pruritus and flare of eczema. Peanut intermittently eaten then stopped because of recurrence of these symptoms. SPT at next visit (30 months of age) was 9mm	Yes	Positive
4. SPT-Negative Stratum	15 months	Peanut-induced irritability and rash; peanut then intermittently eaten. USV[3] performed, SPT 11 mm, OFC not performed. Peanut ingestion stopped.	Yes	Positive
5. SPT Positive Stratum - Baseline SPT 3 mm	11 months	Peanut-induced peri-oral rash. Peanut ingestion stopped. USV performed, SPT 7mm, OFC positive.	Yes	Positive
6. SPT-Negative Stratum	6 months	Peanut-induced SAE (wheezing and angioedema, requiring intramuscular epinephrine). Peanut ingestion stopped. USV performed, initial SPT 1mm, repeat USV SPT 3mm, OFC's not performed. Participant had tolerated peanut on a few occasions prior to SAE.	Yes	Positive
7. SPT-Negative Stratum	10 months	Peanut-induced eczema flares, low and intermittent ingestion reported prior to peanut-induced urticaria and angioedema. Peanut ingestion stopped. SPT at next visit (V12) was 6mm.	Yes	Negative
8. SPT-Negative Stratum	37 months	Peanut-induced pruritus and flare of eczema. SPT at next visit (V30) was 2mm. USV performed, SPT 4mm, OFC positive. Peanut ingestion stopped.	Yes	Negative

9. SPT Positive Stratum - Baseline SPT 1 mm	8 months	Peanut-induced food protein induced enterocolitis syndrome diagnosed by OFC at USV, SPT 1mm (USV was performed because of uncertainty of consumption history). Peanut ingestion stopped.	Yes	Negative

[1] Stratum was determined by a skin prick test to peanut performed as per the study protocol

[2] Oral Food Challenges described are to peanut and performed as per the study protocol

[3] Unscheduled Visit

Table S11. Clinical Symptoms and Medication Requirements Associated with Positive Oral Food Challenges

	Negative Stratum (N=542)		Positive Stratum (N=98)		Overall (N=640)	
	Avoidance Group (N=270)	Consumption Group (N=272)	Avoidance Group (N=51)	Consumption Group (N=47)	Avoidance Group (N=321)	Consumption Group (N=319)
Positive Peanut-Induced Allergic Reactions						
Baseline Challenge (Consumption Group Only)	0 (0)	1 (0.4%)	0 (0)	6 (12.8%)	0 (0)	7 (2.2%)
Diagnostic Criteria at Baseline						
Major Criteria						
Confluent Erythematous Pruritic Rash	0 (0)	1 (100%)	0 (0)	2 (33.3%)	0 (0)	3 (42.9%)
Wheeze, Inability to Speak, Stridor, Dysphonia, and/or Aphonia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
≥3 Urticarial Lesions	0 (0)	1	0 (0)	5 (83.3%)	0 (0)	6 (85.7%)
≥1 Site of Angioedema	0 (0)	0 (0)	0 (0)	1 (16.7%)	0 (0)	1 (14.3%)
Hypotension for Age not Associated with Vasovagal Episode	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Evidence of Severe Abdominal Pain that Persists for ≥3 Hours	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Minor Criteria						
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)	1 (16.7%)	0 (0)	1 (14.3%)
Persistent Rubbing of Nose or Eyes that Lasts for ≥3 Minutes	0 (0)	0 (0)	0 (0)	2 (33.3%)	0 (0)	2 (28.6%)
Persistent Rhinorrhea that Lasts for ≥3 Minutes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Persistent Scratching that Lasts for ≥3 Minutes	0 (0)	1 (100%)	0 (0)	1 (16.7%)	0 (0)	2 (28.6%)
Medication Requirement at Baseline						
Antihistamine	0 (0)	1 (100%)	0 (0)	6 (100%)	0 (0)	7 (100%)
Salbutamol	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ranitidine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Corticosteroid	0 (0)	0 (0)	0 (0)	1 (16.7%)	0 (0)	1 (14.3%)
Adrenaline x1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adrenaline x2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adrenaline x3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other Adrenaline	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Patient Requirement at Baseline						
Hospitalization	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Prolonged Hospitalization	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

	Negative Stratum (N=542)		Positive Stratum (N=98)		Overall (N=640)	
	Avoidance Group (N=270)	Consumption Group (N=272)	Avoidance Group (N=51)	Consumption Group (N=47)	Avoidance Group (N=321)	Consumption Group (N=319)
Positive Peanut-Induced Allergic Reactions						
Visit 60 Challenge	32 (11.9%)	4 (1.5%)	16 (31.4%)	5 (10.6%)	48 (15.0%)	9 (2.8%)
Diagnostic Criteria at Visit 60						
Major Criteria						
Confluent Erythematous Pruritic Rash	4 (12.5%)	0 (0)	3 (18.8%)	1 (20.0%)	7 (14.6%)	1 (11.1%)
Wheeze, Inability to Speak, Stridor, Dysphonia, and/or Aphonia	7 (21.9%)	0 (0)	3 (18.8%)	2 (40.0%)	10 (20.8%)	2 (22.2%)
≥3 Urticarial Lesions	13 (40.6%)	3 (75.0%)	4 (25.0%)	1 (20.0%)	17 (35.4%)	4 (44.4%)
≥1 Site of Angioedema	12 (37.5%)	0 (0)	6 (37.5%)	1 (20.0%)	18 (37.5%)	1 (11.1%)
Hypotension for Age not Associated with Vasovagal Episode	2 (6.3%)	0 (0)	0 (0)	0 (0)	2 (4.2%)	0 (0)
Evidence of Severe Abdominal Pain that Persists for ≥3 Hours	8 (25.0%)	1 (25.0%)	5 (31.3%)	1 (20.0%)	13 (27.1%)	2 (22.2%)
Minor Criteria						
Vomiting	6 (18.8%)	0 (0)	5 (31.3%)	2 (40.0%)	11 (22.9%)	2 (22.2%)
Diarrhea	1 (3.1%)	0 (0)	0 (0)	0 (0)	1 (2.1%)	0 (0)
Persistent Rubbing of Nose or Eyes that Lasts for ≥3 Minutes	12 (37.5%)	2 (50.0%)	8 (50.0%)	2 (40.0%)	20 (41.7%)	4 (44.4%)
Persistent Rhinorrhea that Lasts for ≥3 Minutes	11 (34.4%)	1 (25.0%)	6 (37.5%)	1 (20.0%)	17 (35.4%)	2 (22.2%)
Persistent Scratching that Lasts for ≥3 Minutes	9 (28.1%)	0 (0)	8 (50.0%)	1 (20.0%)	17 (35.4%)	1 (11.1%)
Medication Requirement at Visit 60						
Antihistamine	31 (96.9%)	4 (100%)	16 (100%)	5 (100%)	47 (97.9%)	9 (100%)
Salbutamol	12 (37.5%)	1 (25.0%)	5 (31.3%)	2 (40.0%)	17 (35.4%)	3 (33.3%)
Ranitidine	17 (53.1%)	2 (50.0%)	6 (37.5%)	2 (40.0%)	23 (47.9%)	4 (44.4%)
Corticosteroid	20 (62.5%)	2 (50.0%)	11 (68.8%)	4 (80.0%)	31 (64.6%)	6 (66.7%)
Adrenaline x1	2 (6.3%)	0 (0)	3 (18.8%)	1 (20.0%)	5 (10.4%)	1 (11.1%)
Adrenaline x2	1 (3.1%)	0 (0)	0 (0)	1 (20.0%)	1 (2.1%)	1 (11.1%)
Adrenaline x3	0 (0)	0 (0)	1 (6.3%)	0 (0)	1 (2.1%)	0 (0)
Other Adrenaline	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Patient Requirement at Visit 60						
Hospitalization	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Prolonged Hospitalization	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table S12. Primary Outcome by Race

Primary Outcome Analysis Stratified by Race				
	Peanut Avoidance (N=321)	Peanut Consumption (N=319)	Total (N=640)	p value
Asian				0.012[1]
Not Allergic	5 (55.6%)	15 (100.0%)	20 (83.3%)	
Allergic	4 (44.4%)	0 (0.0%)	4 (16.7%)	
Black				0.025[1]
Not Allergic	20 (76.9%)	22 (100.0%)	42 (87.5%)	
Allergic	6 (23.1%)	0 (0.0%)	6 (12.5%)	
Chinese, Middle Eastern, or Other				0.464[1]
Not Allergic	1 (50.0%)	5 (83.3%)	6 (75.0%)	
Allergic	1 (50.0%)	1 (16.7%)	2 (25.0%)	
Mixed				<0.001[1]
Missing Primary Outcome	1	1	2	
Not Allergic	27 (69.2%)	47 (97.9%)	74 (85.1%)	
Allergic	12 (30.8%)	1 (2.1%)	13 (14.9%)	
White				<0.001[1]
Missing Primary Outcome	6	4	10	
Not Allergic	207 (87.0%)	215 (96.8%)	422 (91.7%)	
Allergic	31 (13.0%)	7 (3.2%)	38 (8.3%)	
Missing Race				
Allergic	0 (0.0%)	1 (100.0%)	1 (100.0%)	

[1]Fisher Exact Test